



## **Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection**

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# Specific Considerations in Antiretroviral Therapy Use in Adolescents with HIV (Last updated April 14, 2020; last reviewed April 14, 2020)

## Panel's Recommendations

- All adolescents living with HIV should receive maximally suppressive antiretroviral (ARV) therapy; this is urgent for those who are sexually active, considering pregnancy, or pregnant **(AII)**.
- ART regimen selection should include consideration of the adolescent's individual needs and preferences **(AIII)**. See [What to Start](#) and [Management of Children Receiving Antiretroviral Therapy](#) for more information.
- All adolescents with HIV should be screened for mental health disorders and substance use disorders **(AII)**.
- Reproductive health issues—including pregnancy intentions, contraceptive methods, safer sex techniques to prevent transmission of HIV and other sexually transmitted infections, pre-exposure prophylaxis for partners, pregnancy planning, and preconception care—should be discussed regularly **(AI)**.
- Providers should be aware of potential interactions between specific ARV medications and hormonal contraceptives that could lower contraceptive efficacy **(AII\*)**.
- Pediatric and adolescent care providers should prepare adolescents for the transition into adult care settings **(AIII)**.

**Rating of Recommendations:** A = Strong; B = Moderate; C = Optional

**Rating of Evidence:** I = One or more randomized trials in children† with clinical outcomes and/or validated endpoints; I\* = One or more randomized trials in adults with clinical outcomes and/or validated laboratory endpoints with accompanying data in children† from one or more well-designed, nonrandomized trials or observational cohort studies with long-term clinical outcomes; II = One or more well-designed, nonrandomized trials or observational cohort studies in children† with long-term outcomes; II\* = One or more well-designed, nonrandomized trials or observational studies in adults with long-term clinical outcomes with accompanying data in children† from one or more similar nonrandomized trials or cohort studies with clinical outcome data; III = Expert opinion

† Studies that include children or children/adolescents, but not studies limited to post-pubertal adolescents

## Background

The majority of individuals in the United States who acquired HIV through perinatal transmission are now adolescents or young adults. Most have had a long clinical course with an extensive antiretroviral treatment (ART) history.<sup>1,2</sup> Many older youth and adults may have initially received nonsuppressive monotherapy or dual-therapy prior to the availability of combination ART regimens, including fixed-dose combination (FDC) formulations. Challenges that affect the treatment of adolescents with perinatally acquired HIV infection include extensive drug resistance, complex regimens, the long-term consequences of HIV and ART exposure,<sup>3</sup> the developmental transition to adulthood, and psychosocial factors.<sup>4-7</sup>

In the United States, most adolescents aged  $\geq 14$  years who recently received HIV diagnoses acquired their infection by horizontal, rather than perinatal, transmission.<sup>8</sup> They generally follow a clinical course similar to that of adults, and the [Adult and Adolescent Antiretroviral Guidelines](#) should be consulted for treatment recommendations for these patients. Additional information that is specific to the care of post-pubertal adolescents can be found in [Adolescents and Young Adults with HIV](#).

## Dosing of Antiretroviral Therapy for Adolescents Living with HIV

Puberty is a time of somatic growth and sexual maturation, with females developing more body fat and males more muscle mass. These physiologic changes may affect drug pharmacokinetics (PKs), which is especially important to consider when determining the dosing for antiretroviral (ARV) drugs that have a narrow therapeutic index (e.g., the protease inhibitor [PI] atazanavir) and that are used in combination with protein-bound medicines or hepatic enzyme inducers or inhibitors.<sup>9</sup>

In addition, many ARV drugs (e.g., abacavir, emtricitabine, lamivudine, tenofovir disoproxil fumarate [TDF], and some PIs) are administered to children at higher body weight-based or body surface area-based doses than would be predicted by direct extrapolation of adult doses. These doses are based on reported PK data

that indicates more rapid drug clearance in children than in adults.

## Timing and Selection of Antiretroviral Therapy

All adolescents living with HIV (like all people living with HIV), should initiate ART as soon as possible. Recommendations for ART dosing in adolescents with sexual maturity ratings (SMRs) between 1 and 3 can be found in [Appendix A: Pediatric Antiretroviral Drug Information](#) and [What to Start](#). Recommendations for initial therapy for adolescents and young adults with SMRs between 4 and 5 are available in the What to Start section of the Adult and Adolescent Antiretroviral Guidelines. **Optimizing and simplifying treatment may be especially important when treating adolescents, as this can help improve adherence (see [Modifying Antiretroviral Regimens in Children with Sustained Virologic Suppression on Antiretroviral Therapy](#)).**

Clinicians who are treating adolescents of childbearing potential should consider additional factors before initiating ART, including potential drug interactions with contraception and the safety of using certain ARV drugs before conception or during pregnancy (see the Contraception, Pregnancy, and Antiretroviral Therapy section below).

## Adherence Concerns in Adolescents

Poor adherence to ART is a common problem among adolescents with HIV. Both psychosocial and cognitive developmental factors may contribute to adherence challenges and should be assessed regularly. The adolescent's individual needs and preferences should also be considered when making decisions about initiating or changing ART. Comprehensive systems of care are required to serve both the medical and psychosocial needs of adolescents with HIV, as they are frequently inexperienced with managing their own health care and may lack health insurance. **Adolescents with perinatally acquired HIV infection are at risk for neurocognitive impairment, which can also interfere with medication adherence.**<sup>10</sup> Many are also at risk for mental health co-morbidities, including psychiatric, behavioral, and substance use disorders that may interfere with adherence to ART.<sup>11,12</sup> Compared with adults, youth have lower rates of viral suppression and higher rates of virologic rebound and loss to follow up.<sup>13-15</sup> For further discussion of interventions to promote adherence in adolescents, see the [Adolescents and Young Adults with HIV](#) section of the Adult and Adolescent Antiretroviral Guidelines and a 2013 review by Agwu and Fairlie.<sup>3</sup>

A specific challenge is presented by youth who, despite interventions, remain unable to adhere to therapy. In these cases, alternatives to changing the ARV regimen can include, but are not limited to: simplifying treatment to a once-daily regimen or an FDC tablet, using cell phone alerts and other eHealth approaches to remind patients to take their medication and attend clinic visits, initiating a short-term deferral of treatment until adherence improves or while adherence-related problems are aggressively addressed, initiating an adherence testing and training period in which a placebo (e.g., vitamin pill) is administered, scheduling appointments more frequently, employing directly observed therapy, and avoiding regimens with a low genetic resistance threshold. Such decisions should be individualized, and the patient's clinical and laboratory status should be monitored carefully. **The use of long-acting oral and injectable ARV regimens for adolescents are currently being investigated, and these regimens may provide an alternative approach for adolescents with adherence challenges.**

## Mental Health and Substance Use Concerns in Adolescents

Many factors can increase the risk of adverse mental health outcomes among adolescents with perinatally acquired HIV, including long-term medical treatment for a chronic disease, hospitalizations, stigma, the neurocognitive impacts of HIV, parental psychiatric and substance use disorders, and family and caregiver stress and loss. The prevalence of mental health disorders in youth with perinatally acquired HIV is high, with nearly 70% of these adolescents meeting the criteria for a psychiatric disorder at some point in their lives.<sup>11,16-18</sup> The most common conditions include anxiety and behavioral disorders, mood disorders (including depression), and attention-deficit/hyperactivity disorder. Effectively managing psychiatric comorbidities can improve a patient's adherence to medical care, including ART, and lead to better academic

performance and interpersonal relationships (see [Substance Use Disorders and HIV](#) in the Adult and Adolescent Antiretroviral Guidelines).<sup>12,19-21</sup>

Interventions that address mental health in youth with perinatally acquired HIV include pharmacologic interventions; behavioral modification; and individual, family, and group counselling. However, there is a lack of data on the effectiveness of these interventions on HIV clinical outcomes.<sup>22-24</sup> **Current evidence suggests that a combination of tailored psychotherapy (such as cognitive behavioral therapy) and pharmacotherapy can reduce depressive symptoms in adolescents with HIV; however, clinicians who prescribe pharmacotherapy for depression must take potential interactions with ARV drugs into account.**<sup>25,26</sup> Providers who are caring for adolescents with HIV should incorporate screening for psychiatric and substance use disorders into routine care and refer patients to age-appropriate services as needed. The [American Academy of Pediatrics](#) policy statement provides some guidance and screening tools, particularly for depression. Screening tools for substance use, such as [Screening, Brief Intervention, and Referral to Treatment \(SBIRT\)](#) or [Car, Relax, Alone, Forget, Friends, and Trouble \(CRAFT\)](#), may be used. Providers should also consider emerging substance use trends when screening adolescents.<sup>27</sup> **Further guidance on screening tools for substance use and mental health is provided by the [National Institute on Drug Abuse's Screening and Assessment Tools Chart](#).**

## Sexually Transmitted Infections in Adolescents

Clinicians should discuss the risk of sexually transmitted infections (STIs) with their patients. All adolescents with HIV should be screened for STIs and treated appropriately. Clinicians should regularly obtain a detailed sexual history for adolescents in order to determine which STI screening tests are appropriate. In young men who have sex with men, screening for STIs often requires sampling from several body sites, including the oropharynx, rectum, and urethra, since multiple sites of infection are common. Furthermore, a negative assay at a single site does not exclude infection at another site.<sup>28</sup> For a more detailed discussion of STIs, see the most recent Centers for Disease Control and Prevention guidelines,<sup>29</sup> [Human Papillomavirus Disease](#) in the Adult and Adolescent Opportunistic Infection Guidelines, and [Human Papillomavirus](#) in the Pediatric Opportunistic Infection Guidelines. All female adolescents with HIV who are sexually active should receive gynecologic services. All adolescents should receive three doses of the 9-valent human papillomavirus vaccination.

## Contraception, Pregnancy, and Antiretroviral Therapy

Adolescents with HIV may initiate sexual activity before or after puberty. Sexually active adolescents are at risk for unintended pregnancy. Approximately half of pregnancies in the United States, including those among women with HIV, are unintended or unplanned.<sup>30,31</sup> Providers should regularly assess adolescents' desires to become pregnant or avoid pregnancy (also known as their pregnancy intentions). Family planning counseling, including a discussion of the risks of sexual HIV transmission, perinatal HIV transmission, and methods for reducing these risks, should be provided to all youth. Reproductive health options, such as pregnancy planning, preconception care, contraceptive methods, pre-exposure prophylaxis for partners, and safer sex techniques (including instruction on the correct and consistent use of condoms) for prevention of sexual HIV transmission, should be discussed regularly (see [U.S. Medical Eligibility Criteria for Contraceptive Use](#)).<sup>32</sup> For additional information, refer to the following sections of the Perinatal Guidelines: [Preconception Counseling and Care for Women of Childbearing Age Living with HIV](#) and [Reproductive Options for Couples When One or Both Partners are Living with HIV](#). The American Academy of Pediatrics Committee on Adolescence offers guidance about the integration of sexual and reproductive health care in pediatric clinical settings.<sup>33</sup>

The possibility of planned and unplanned pregnancy should be considered when selecting an ART regimen for a female adolescent. The most vulnerable period in fetal organogenesis is the first trimester, often before pregnancy is recognized. When treating adolescents of childbearing potential, clinicians should carefully

review the potential toxicities of ARV drugs and consider making any necessary changes to a regimen as promptly as possible (e.g., before conception, when possible). For additional information, please see the [Teratogenicity](#) section of the Perinatal Guidelines. Readers should consult [Table 5](#) in the [Recommendations for Use of Antiretroviral Drugs During Pregnancy](#) section of the Perinatal Guidelines for information about the selection and management of ARV drugs before and during pregnancy for women with HIV who are of childbearing age. **Exposure to dolutegravir (DTG) around the time of conception has been associated with a small, but significant, increase in the risk of infant neural tube defects that** should be considered when discussing ART options with female adolescents and their caregivers. Specific recommendations about the initiation and use of DTG in adolescents and women of childbearing potential and in those who are pregnant **or trying to conceive** are available in the Adult and Adolescent Antiretroviral Guidelines (see [Table 6b](#) and [Adolescents and Young Adults with HIV](#)) and in the Perinatal Guidelines (see [Teratogenicity, Recommendations for Use of Antiretroviral Drugs During Pregnancy](#), and [Appendix D: Dolutegravir Counseling Guide for Health Care Providers](#)).

### ***Interactions Between Contraceptives and Antiretroviral Drugs***

Women with HIV can use all available contraceptive methods, including hormonal contraceptives, implantable devices, intrauterine devices, the transdermal patch, and vaginal ring.<sup>34</sup>

Several PIs and non-nucleoside reverse transcriptase inhibitors alter the metabolism of oral contraceptives, which may theoretically reduce the efficacy of oral contraceptive agents or increase the risk of estrogen-related or progestin-related adverse effects (see [Drug-Drug Interactions](#) in the [Adult and Adolescent Antiretroviral Guidelines](#) and the [HIV Drug Interaction Checker](#)).<sup>35-37</sup> Integrase strand transfer inhibitors (specifically raltegravir) appear to have no interaction with estrogen-based contraceptives.<sup>38</sup> For more information about potential interactions between ARV drugs and hormonal contraceptives, please see [Table 3](#) in the Perinatal Guidelines.

Concerns about loss of bone mineral density with long-term use of depot medroxyprogesterone acetate (DMPA), with or without coadministration of ART (specifically TDF), should not preclude the use of DMPA as an effective contraceptive, unless there is clinical evidence of bone fragility.

### ***Pregnant Adolescents Living with HIV***

Adolescents who want to become pregnant should receive preconception counseling and care, including a discussion of pregnancy planning and special considerations when using ARV drugs during pregnancy (see the [Perinatal Guidelines](#)). Pregnancy should not preclude the use of optimal therapeutic regimens. Clinicians need to consider maternal and fetal safety as well as the need to prevent perinatal transmission when selecting regimens for pregnant women or women who are planning to become pregnant. See the [Perinatal Guidelines](#) for more details about choosing an ARV regimen for pregnant women with HIV, including adolescents, and guidance regarding the use of DTG during pregnancy. Pregnancies can be expected as girls with perinatally acquired HIV enter adolescence and young adulthood.<sup>39,40</sup> Some studies suggest higher rates of adverse pregnancy outcomes, such as small-for-gestational-age infants, among pregnant women with perinatally acquired HIV than among those who acquired HIV by horizontal transmission, and unplanned pregnancy appears to be a frequent occurrence.<sup>40-42</sup> However, the rate of perinatal transmission among pregnant women with perinatally acquired HIV who are receiving ART appears to be similar to the rate among women on ART who acquired HIV by horizontal transmission.<sup>43-47</sup>

### ***Special Considerations for Adolescents with HIV Who Are Sexual Minorities***

**Adolescence represents a period of emerging recognition of sexual identity. Adolescents who are lesbian, gay, bisexual, transgender, or nonbinary and who are living with HIV require both culturally competent providers and tailored medical care. Health care providers should ask patients nonjudgmental questions about their sexual and gender identity to determine whether they require specific medical and support services. It is important to consider the possibility of drug-drug interactions in adolescents who are receiving both ART and**



gender-affirming hormone therapy. Additional resources for the care of these adolescents can be found in the [Adolescents and Young Adults with HIV](#) section and the [Transgender People with HIV](#) section of the [Adult and Adolescent Antiretroviral Guidelines](#).

## Transitioning Adolescents into Adult HIV Care Settings

Facilitating a seamless transition for adolescents with HIV from their pediatric/adolescent care clinic to adult care is important but challenging.<sup>48-50</sup> Many adolescents disengage from care during the transition to adult care, putting them at risk for HIV progression and transmission to partners.<sup>51-53</sup> Pediatric and adolescent care providers and their multidisciplinary teams should have a formal written plan in place to transition adolescents to adult care. While transition generally occurs when individuals are in their late teens or early 20s, discussion of and planning for the transition process should be initiated early in the teen years, with involvement from both the adolescent and their parents and/or caregivers. A 2005 study described transition as “a multifaceted, active process that attends to the medical, psychosocial, cognitive and educational, or vocational needs of adolescents as they move from the child- to the adult-focused health care system.”<sup>54</sup> Care models for children and adolescents with perinatally acquired HIV tend to be family-centered, consisting of a multidisciplinary team that often includes physicians, nurses, social workers, and mental health professionals. These providers generally have long-standing relationships with patients and their families, and care is rendered in discreet, intimate settings. Although expert care is also provided under the adult HIV care medical model, adolescents and their caregivers may be unfamiliar with the busier, more individual-centered clinics that are typical of adult medical care providers. These providers often expect patients to assume a greater level of responsibility for their care, and adolescents may be uncomfortable with providers with whom they do not have a long-standing relationship.

One multisite study in the United States found that adolescents who transitioned to adult care at an older age reported greater satisfaction with their care than those who transitioned at a younger age. Additionally, adolescents who reported being able to perform certain tasks that were related to their care (e.g., making appointments, requesting prescriptions, arranging transportation to appointments) were more likely to be engaged in adult care.<sup>55</sup> Providing adolescents, caregivers, and their new adult medical care providers with support and guidance regarding the expectations for each person involved in the patient-provider relationship may be beneficial. In this situation, it may be helpful for a pediatric care provider and an adult care provider to share joint care of a patient for a period of time.

Adolescent care providers should have a candid discussion with the transitioning adolescent and their caregivers to understand what qualities the adolescent considers most important when choosing an adult care setting (e.g., confidentiality, small clinic size, low patient-to-provider ratio, availability of after-school or evening appointments). Social determinants, such as the patient’s developmental status, behavioral/mental health co-morbidities, housing, family support, employment status, recent discharge from foster care, peer pressure, illicit drug use, and incarceration, should be considered during transition.

Currently, there is no definitive model of transition to adult HIV care, and only a limited number of studies have reported on outcomes following transition, though research in this area is ongoing. **Recent studies have shown potential for successful transition and ongoing retention using models that include a multidisciplinary approach that utilizes internal medicine/pediatric-trained providers, peer navigators, social workers, mental health support, and a youth-focused care model for adolescents who were already attending adult HIV clinics.**<sup>56,57</sup> Several studies have shown that youth who transitioned into adult care settings had higher rates of attrition from care than those who remained in pediatric/adolescent care; in one U.S. study, only 42% of youth receiving care in an adult clinic remained in care after 12 months compared to 75% of those receiving care in a pediatric clinic. Another multisite study in the United States showed that only 37% of youth had successfully transitioned to adult care after a follow-up period of 9 months.<sup>15,52</sup> A report from the United Kingdom suggests that the mortality rate of adolescents with HIV increases after transition.<sup>20,53</sup> In a report on 50 youth from a Baltimore clinic (31 with non-perinatally acquired HIV and 19 with perinatally acquired HIV), only 50% were retained in care 12 months after transition, although 86% of participants were

successfully transitioned and linked to adult care.<sup>51</sup> Another study used surveillance data in New York City to examine the continuum of care for youth with perinatally acquired HIV. Rates of continuous engagement in care and viral suppression were 89% and 67%, respectively, for individuals aged 13 years to 19 years. These rates decreased to 76% and 58% for those aged 20 years to 29 years, underscoring the need to critically examine transition and determine the best mechanisms to optimize the long-term outcomes for youth with perinatal HIV infection.<sup>2</sup> A recent retrospective study from Atlanta reported that, while retention rates were initially high when adolescents entered adult care, they had declined significantly by the second year after transition. Pre-transition viral suppression and shorter linkage time between the pediatric and adult clinic were associated with better outcomes post-transition.<sup>53</sup>

Some general guidelines, mostly based on anecdotal evidence and consensus expert opinion, are available about transition plans and who might benefit most from them.<sup>49,58-65</sup> To maximize the likelihood of success, providers should prepare adolescents for transition long before it occurs. Attention to the following key areas could improve retention in care and minimize the risk of ART interruptions:

- Educating HIV care teams and staff about transitioning;
- Beginning discussions about transition early, before the actual transition process;
- Developing a written, individualized transition plan to address comprehensive care needs, including medical, psychosocial, and financial aspects of transitioning;
- Optimizing communication between providers at pediatric/adolescent clinics and providers at adult clinics;
- Identifying adult care providers who are experts in providing care to adolescents and young adults;
- Addressing barriers caused by a lack of information, stigma, or disclosure concerns;
- Discussing the differences between the practice styles of adult clinics and pediatric/adolescent clinics;
- Helping youth develop the skills needed to manage their own care, including counseling them on appointment management, the appropriate use of a primary care provider, the importance of prompt symptom recognition and reporting, and the importance of managing medications, insurance, and state and federal benefits;
- Identifying an optimal clinic model for a given setting (e.g., simultaneous transition of mental health and/or case management services versus a gradual phase-in);
- Clearly defining the desired outcomes for the transition, such as retention in care, ongoing access to other services (e.g., case management, mental health), clinical outcomes (e.g., viral suppression), and patient satisfaction;
- Implementing ongoing evaluations to measure the success of a transition model;
- Engaging in regular multidisciplinary case conferences between adult and adolescent care providers;
- Implementing interventions that may be associated with improved outcomes, such as support groups and mental health consultation; *and*
- Identifying a care navigator who can provide support during the transition.

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